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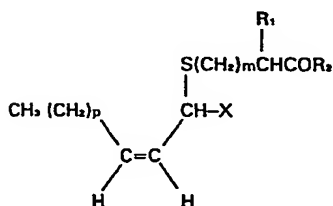
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(54) Substituted unsaturated mercaptocarboxylic acids and derivatives as leukotriene antagonists.

(57) The compounds represented by the formula (I)



(I)

wherein m is 0, 1 or 2; p is 9, 10, 11, 12 or 13; R₁ is

hydrogen, amino or -NHCH₂CO₂H; R₂ is hydroxyl, amino, -NHCH₂CO₂H, -NCH₂CO₂H, -NHCHCO₂H, -NHCHCO₂H or

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{NHCH}_2\text{CONH}_2 \end{array}$,
 $\begin{array}{c} \text{CH}_2 \\ | \\ \text{NHCH}_2\text{CONH}_2 \end{array}$,
 $\begin{array}{c} \text{CH}(\text{CH}_3)_2 \\ | \\ \text{OH} \end{array}$

and X is -CO₂H, -CH₂OH, -CHCH₂OH

or -CH(CH₂)_nCOR, wherein n is 1 or 2, Y is hydrogen or

$\begin{array}{c} \text{Y} \\ | \\ \text{hydroxyl or amino} \end{array}$
 with the proviso that when m is 0, R₁ is hydrogen, or pharmaceutically acceptable salt thereof have been found to be leukotriene antagonists and useful in the treatment of diseases in which leukotrienes are a factor, such as asthma.

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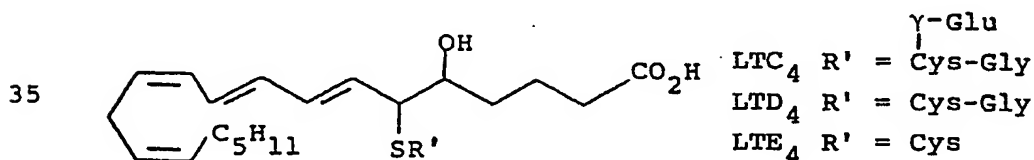
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LEUKOTRIENE ANTAGONISTS

BACKGROUND OF THE INVENTION

"Slow Reacting Substance of Anaphylaxis" (SRS-A) has been shown to be a highly potent bronchoconstricting substance which is released primarily from mast cells and basophils on antigenic challenge. SRS-A has been proposed as a primary mediator in human asthma. SRS-A, in addition to its pronounced effects on lung tissue, also produces permeability changes in skin and may be involved in acute cutaneous allergic reactions. Further, SRS-A has been shown to effect depression of ventricular contraction and potentiation of the cardiovascular effects of histamine.

The discovery of the naturally occurring leukotrienes and their relationship to SRS-A has reinforced interest in SRS-A and other arachidonate metabolites. SRS-A derived from mouse, rat, guinea pig and man have all been characterized as mixtures of leukotriene-C₄ (LTC₄), leukotriene-D₄ (LTD₄) and leukotriene-E₄ (LTE₄); the structural formulae of which are represented below.



DETAILED DESCRIPTION OF THE INVENTION

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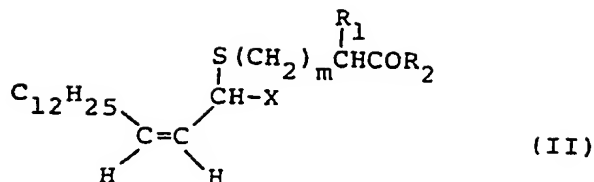
hydrogen, amino or $\text{-NH}\overset{\text{O}}{\parallel}\text{CCH}_3$; R_2 is hydroxyl, amino,
 20 $\text{-NHCH}_2\text{CO}_2\text{H}$, $\text{-NCH}_2\text{CO}_2\text{H}$, $\text{-NHCHCO}_2\text{H}$, $\text{-NHCHCO}_2\text{H}$ or
 $\text{-NHCH}_2\text{CONH}_2$; and x is $\text{-CO}_2\text{H}$, $\text{-CH}_2\text{OH}$, $\text{-CHCH}_2\text{OH}$
 CH_3 CH_3 $\text{CH(CH}_3)_2$
 OH

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wherein m, R₁, R₂ and X are described above.

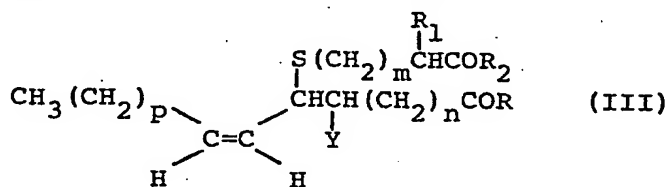
The compounds of formula (II) wherein X is
 10 -CO₂H are 3(Z)-hexadecenoic acid derivatives which are
 exemplified by 2-[(2-carboxyethyl)thio]-3(Z)-hexadecenoic
 acid.

The compounds of formula (II) wherein X is
 -CH₂OH are 3(Z)-hexadecen-1-ol derivatives which are
 15 exemplified by 2-[(2-carboxyethyl)thio]-3(Z)-hexadecen-
 1-ol.

The compounds of the formula (II) wherein X is
 -CHCH₂OH are 4(Z)-heptadecen-1,2-diol derivatives which
 20 are exemplified by 3-[(2-carboxyethyl)thio]-4(Z)-
 heptadecen-1,2-diol.

The compounds of formula (I) wherein X is
 -CH(CH₂)_nCOR in which n, Y and R are described above
 25 are represented by the formula (III)

30



wherein m, n, p, Y, R, R₁, and R₂ are described above.

The compounds of formula (III) wherein n is 2 and
 35 p is 11 have a C₁₉ carbon skeleton and are designated
 6(Z)-nonadecenoic acid derivatives. Similarly, when n is

1 1 and p is 11, the compounds of formula (III) have a C₁₈
carbon skeleton and are designated 5(Z)-octadecenoic acid
derivatives. When n is 2 and p is 9 the compounds of
formula (III) have a C₁₇ carbon skeleton and are
5 designated 6(Z)-heptadecenoic acid derivatives. Also,
when n is 2 and p is 13 the compounds of formula (III)
have a C₂₁ carbon skeleton and are designated
6(Z)-heneicosenoic acid derivatives.

The 6(Z)-nonadecenoic acid derivatives of the
10 compounds of formula (III) wherein R is hydroxyl and Y is
hydroxyl contain two asymmetric centers, one of which is
at carbon atom 4 (i.e. the hydroxyl substituted carbon
atom) and one of which is at carbon atom 5 (i.e. the thiol
substituted carbon atom). This leads to the possibility
15 of four stereoisomers for each compound. In practice, the
compounds of this invention of formula (III) have been
prepared in a mixture of two stereoisomers, that is the
4R, 5S isomer and the 4S, 5R isomer. The individual pure
stereoisomers are obtainable by preparative high pressure
20 liquid chromatography (HPLC) separation of the appropriate
intermediate compounds if those compounds possess a third
asymmetric center. In the cases where a third asymmetric
center is not available in the synthetic pathway of the
desired compounds, one may be introduced by employing an
25 asymmetric protecting group, such as an N-trifluoroethoxy-
carbonyl-i-prolyl ester. After separation of the
individual stereoisomer, the protecting group is removed
by standard procedures.

The 6(Z)-nonadecenoic acid derivatives of formula
30 (III) are exemplified by the following compounds as the
4R, 5S isomer, the 4S, 5R isomer or mixture of the two
isomers:

4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-
nonadecenoic acid;

35 5-[(3-carboxymethylamino-3-oxopropyl)-
thio]-4-hydroxy-6(Z)-nonadecenoic acid;

1 5-[(2-amino-3-carboxymethylamino-3-oxopropyl)thio]-
4-hydroxy-6(Z)-nonadecenoic acid;

 5-[(3-carboxymethyl-N-methylamino-3-oxopropyl)-
thio]-4-hydroxy-6(Z)-nonadecenoic acid;

5 5-[(2-amino-3-carboxamidomethylamino-3-oxo-
propyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid;

 4-hydroxy-5-[(carboxymethyl)thio]-6(Z)-
nonadecenoic acid;

 5-[[2-(aminocarbonyl)ethyl]thio]-4-hydroxy-6(Z)-
10 nonadecenoic acid;

 4-hydroxy-5-[(2-amino-2-carboxyethyl)thio]-6(Z)-
nonadecenoic acid; and

 4-hydroxy-5-[(3-carboxypropyl)thio]-6(Z)-
nonadecenoic acid.

15 The 5(Z)-octadecenoic acid derivatives of the
compounds of formula (III) wherein Y is hydroxyl are also
contain two asymmetric centers at carbon atom 3 and carbon
atom 4 and thus the possibility of four stereoisomers for
each compound exists.

20 Specific compounds of the formula (III) are those
5(Z)-octadecenoic acid derivatives exemplified by the
following compounds as a mixture of the four isomers:

 3-hydroxy-4-[(2-carboxyethyl)thio]-5(Z)-
octadecenoic acid.

25 Also representative of the compounds of formula
(III) is 4-[(2-carboxyethyl)thio]-5(Z)-octadecenoic acid.

 The compounds of the formula (III) wherein Y is
hydrogen are exemplified by 5-[(2-carboxyethyl)thio]-6(Z)-
nonadecenoic acid.

30 Specific compounds of the formula (III) are those
6(Z)-nonadecenoic acid derivatives wherein R is amino and
Y is hydroxyl are exemplified by 5-[(3-carboxymethylamino-
3-oxopropyl)thio]-4-hydroxy-6(Z)-nonadecenamide and
4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-nonadecenamide.

35 Additional compounds of the formula (III) are
those 6(Z)-heptadecenoic acid derivatives which are

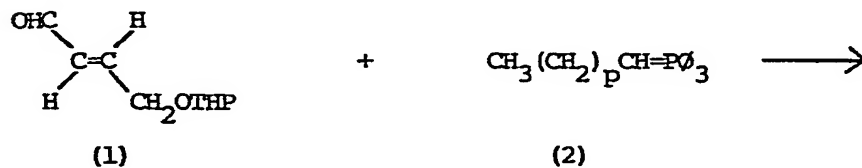
1 exemplified as a mixture of isomers of 4-hydroxy-5-
[(2-carboxyethyl)thio]-6(Z)-heptadecenoic acid.

Further compounds of the formula (III) are those
6(Z)-heneicosenoic acid derivatives wherein R is hydroxyl
5 and X is hydroxyl which are exemplified as a mixture of
isomers of 4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-
heneicosenoic acid.

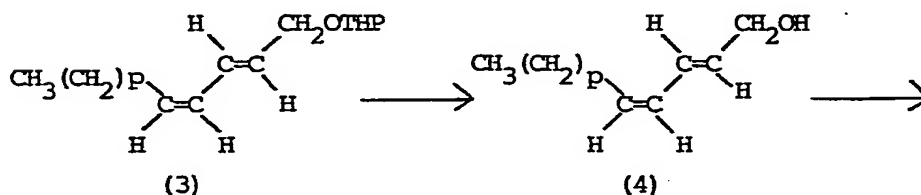
The compounds of formula (I) wherein X is
-CO₂H, -CH₂OH and -CH(OH)CH₂OH are prepared via the
10 following synthetic pathways starting with 4-hydroxybut-
2(E)-ene-1-al tetrahydropyranyl ether (1), wherein THP is
a tetrahydropyranyl radical, as follows:

Pathway A

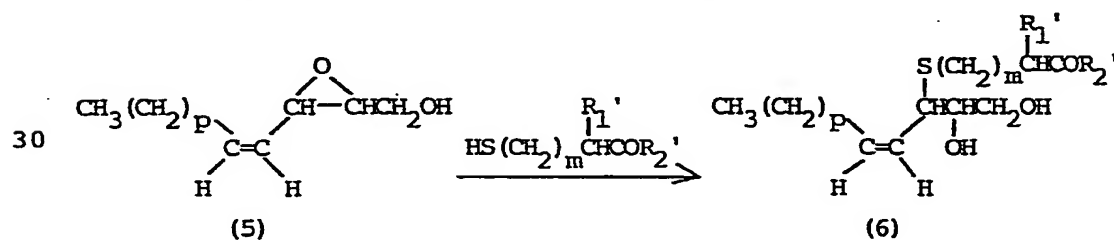
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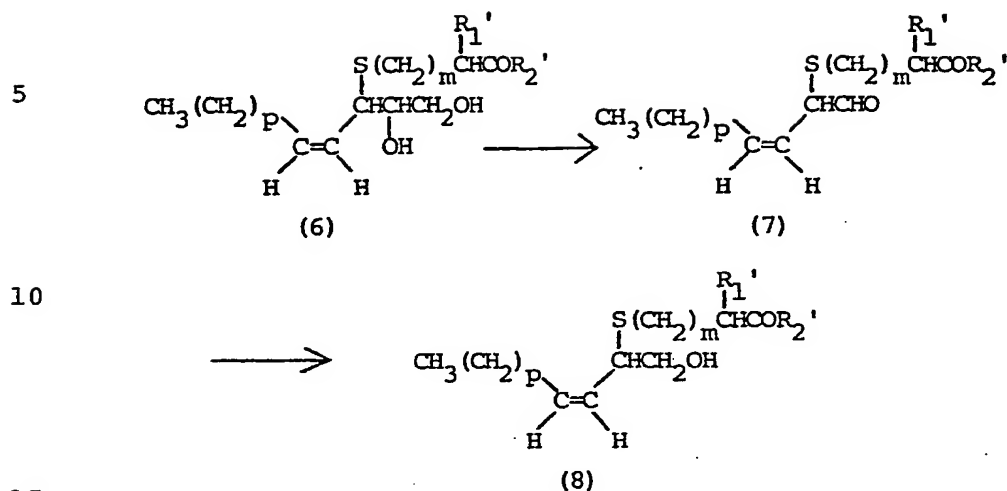
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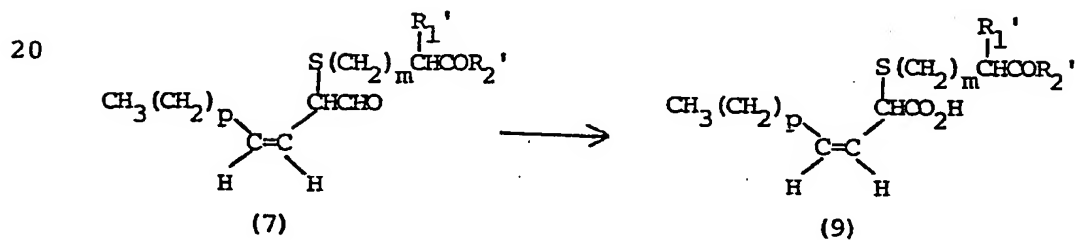
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1 Pathway B



Pathway C



Compound (1), which is a known compound, is reacted with the appropriate alkyltriphenyl phosphonium ylid under Wittig conditions to yield compound (3).

30 Compound (3) is hydrolyzed to cleave the THP ether and gives compound (4) which is epoxidized to afford compound (5). Compound (5) is reacted with the appropriate mercaptan, wherein R_1' and R_2' are R_1 and R_2 respectively as described above or a radical which is

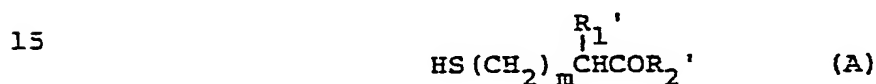
35 easily converted into the desired substituent, such as an alkyl ester or trifluoromethylacetamide, to give compound

1 (6). Compound (6) may either (a) be easily converted into compounds of the formula (I) wherein X is $\begin{array}{c} -\text{CHCH}_2\text{OH} \\ | \\ \text{OH} \end{array}$

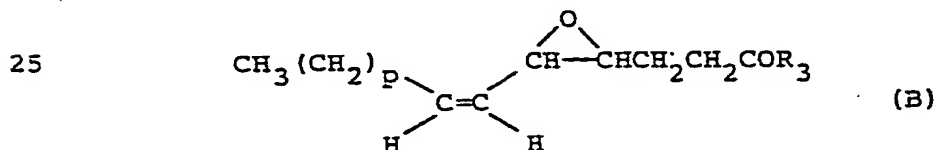
or analogs thereof; or (b) oxidatively cleaved to compound

5 (7). Compound (7) may either (a) be reduced to compound (8) which is easily converted to compounds of the formula (I) wherein X is $-\text{CH}_2\text{OH}$ or analogs thereof or (b) oxidized to compound (9) which is easily converted into compounds of the formula (I) wherein X is $-\text{CO}_2\text{H}$ or
10 analogs thereof.

The compounds of the formula (III) wherein n is 2 and Y is hydroxy are readily prepared by reacting the appropriate thiol containing compound of the formula (A)



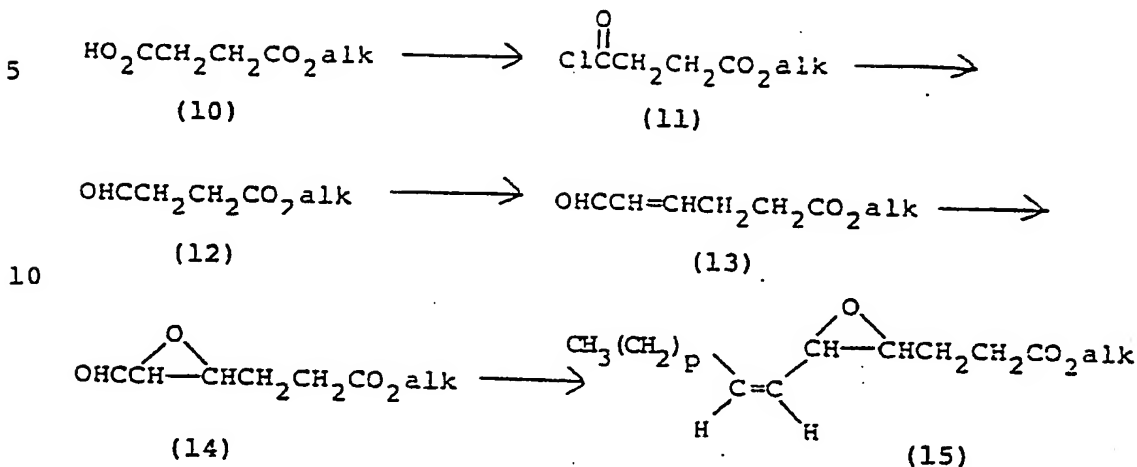
wherein m is described above and R_1' and R_2' are respectively R_1 and R_2 or a radical easily convertible
20 to the desired substituent, such as an alkyl ester or trifluoromethylacetamide, with a 4,5-epoxy-6(Z)-alkenoic acid derivative of the formula (B)



30 wherein p is described above and R_3 is R or a radical which is easily convertible into the desired acid moieties, such as CO_2alk wherein alk is a lower alkyl group. The thiol containing compounds of formula (A) are known or easily prepared from known compound utilizing
35 standard chemical transformations. The 4,5-epoxy-6(Z)-alkenoic acid derivatives (B) are readily prepared from

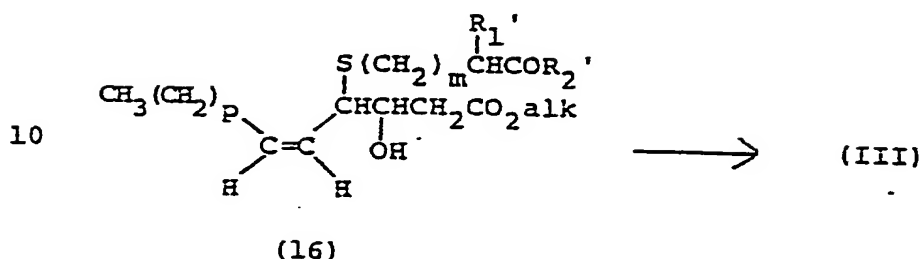
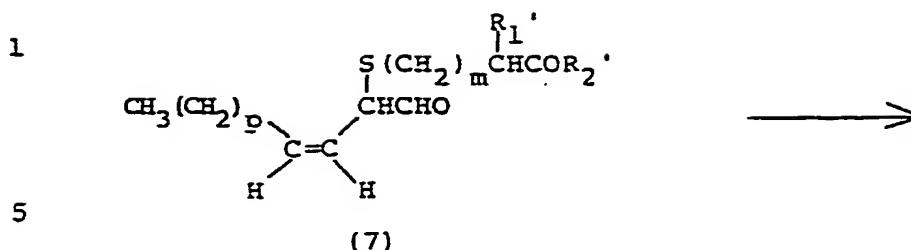
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1 monoalkyl succinate (10) via the following synthetic pathway:



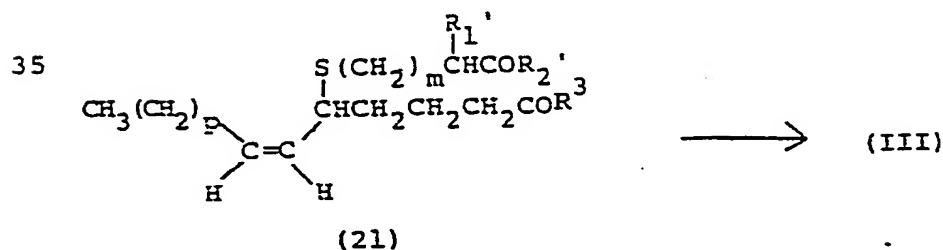
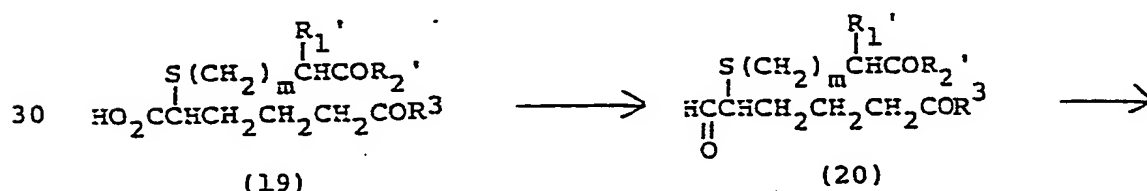
15 Mono-methyl succinate (10), wherein alk is methyl, was chlorinated with oxalyl chloride in dimethyl methyl, was chlorinated with oxalyl chloride in dimethyl
20 formamide and methylene chloride to afford 3-carbo- methoxypropionyl chloride (11). Compound (11) was catalytically hydrogenated over palladium-charcoal catalyst in the presence of 2,6-lutidine to yield 3-carbomethoxypropionaldehyde (12) which was reacted with
25 formylmethylene triphenylphosphorane under Wittig reaction conditions to obtain 5-carbomethoxy-2-pentenal (13). Compound (13) was epoxidized with aqueous hydrogen peroxide in the presence of 1N sodium bicarbonate to afford methyl-4,5-epoxy-6-oxohexanoate (14). Compound (14) is reacted with alkyltriphenylphosphonium ylid to
30 give methyl-4,5-epoxy-6(Z)-alkenoate (15).

The 5(Z)-alkenoic acid derivatives of the formula (III) wherein n is 1 and Y is hydroxy are prepared via the synthetic pathway starting from 2-[(2-carbomethoxyethyl)-thio]-3(Z)-alkenal (7) as follows:



Compound (7) is reacted with methyl acetate in the presence of lithium diisopropylamide to give methyl-3-hydroxy-4-[(2-carbomethoxyethyl)thio]-5(Z)-alkenoate (16) which is saponified to afford compound of the formula (III) wherein m is 1, R is hydroxyl, R₁ is hydrogen and R₂ is hydroxyl.

The 6(Z)-nonadecenoic acid derivatives of formula (III) wherein n is 2 and Y is hydrogen are prepared via the pathway starting from 5-substituted pentanoic acids (17) as follows:



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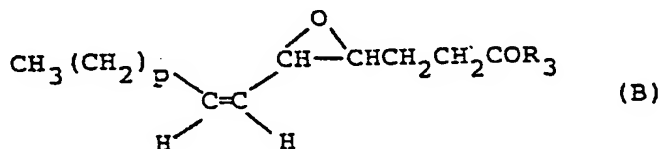
- 1 For example, 5-carbomethoxypentanoic acid (17), wherein R^3
 is O-methyl, was reacted with thionyl chloride and then
 N-bromosuccinimide (NBS) followed by base hydrolysis to
 give 2-bromo-5-carbomethoxypentanoic acid (18). Compound
 5 (18) was reacted with methyl-3-mercaptopropionate ($m = 1$,
 $R_1' = H$ and $R_2' = OCH_3$) to yield 5-carbomethoxy-2-
 [(2-carbomethoxyethyl)thio]-pentanoic acid (19). Compound
 (19) reacted first with diborane and then with dimethyl-
 sulfoxide and trifluoroacetic anhydride to afford
 10 5-carbomethoxy-2-[(2-carbomethoxyethyl)thio]-pentanal
 (20). Compound (20) was reacted under Wittig conditions
 with alkyltriphenylphosphonium ylid to yield methyl-
 5-[(2-carbomethoxyethyl)thio]-6(Z)-alkenoate (21) which is
 saponified to afford a compound of the formula (III)
 15 wherein m is 1, R_1 is hydrogen, and R_2 is hydroxyl.

The 5(Z)-octadecenoic acid derivatives of the
 formula (III) wherein n is 1 and Y is hydrogen can be
 prepared via the general synthetic pathway utilized for
 the preparation of the 6(Z)-nonadecenoic acid derivatives
 20 but starting from 4-substituted butanoic acid.

The compounds of the formula (III) wherein R is
 amino can be prepared by initially forming the γ -lactone
 of the appropriate compound of formula (III) with
 trifluoroacetic anhydride and then reacting the γ -lactone
 25 with ammonia to afford the desired amide.

The instant invention also includes the 4,5-epoxy-
 6(Z)-alkenoic acid derivatives of the formula (B)

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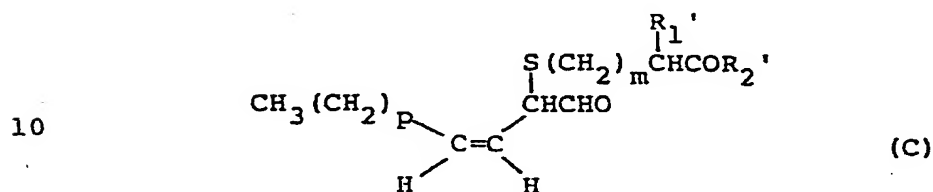


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1 wherein p is 9, 10, 11, 12 or 13 and R₃ is R or a radical which is easily convertible into R such as Oalk wherein alk is an alkyl radical containing one to six carbon atoms.

5 Additionally, this invention includes the compounds of the formula (C)



15 wherein m is 0, 1 or 2; p is 9, 10, 11, 12 or 13; R₁' is hydrogen, -NH $\overset{\text{O}}{\parallel}$ CCF₃ or -NH $\overset{\text{O}}{\parallel}$ CCH₃ and R₂' is amino, -NHCH₂CO₂R₃', -N $\underset{\text{CH}_3}{\text{CH}}$ ₂CO₂R₃', -NH $\underset{\text{CH}_3}{\text{CH}}$ CHCO₂R₃', -NH $\underset{\text{CH}(\text{CH}_2)_3}{\text{CH}}$ CHCO₂R₃', -NHCH₂CONH₂ or OR₃' wherein R₃' is an alkyl radical containing one to six carbon atoms with the proviso that when m is 0, R₁' is hydrogen.

20 The compounds of the formulae (B) and (C) possess the double bond in the cis conformation. The structural similarities between these compounds and the compounds of the formula (I) contribute to the leukotriene antagonist properties of the compounds of formula (I).

30 The leukotriene antagonist activity of the compounds of this invention is measured by the ability of the compound to inhibit leukotriene induced contraction of guinea pig tracheal tissues in vitro and to inhibit leukotriene induced bronchoconstriction in guinea pigs in vivo. The following methodologies were employed:
In vitro: Guinea pig (adult male albino Hartley strain) tracheal spiral strips of approximate dimensions 2 to 3 mm cross-sectional width and 3.5 cm length were bathed in modified Krebs buffer in jacketed 10 ml tissue bath and

- 1 continuously aerated with 95% O₂/5% CO₂. The tissues
were connected via silk suture to force displacement
transducers for recording isometric tension. The tissues
were equilibrated for 1 hr., pretreated for 15 minutes
5 with meclofenamic acid (1 μM) to remove intrinsic
prostaglandin responses, and then pretreated for an
additional 30 minutes with either the test compound or
vehicle control. A cumulative concentration-response
curve for LTD₄ on triplicate tissues was generated by
10 successive increases in the bath concentration of the
LTD₄. In order to minimize intertissue variability, the
contractions elicited by LTD₄ were standardized as a
percentage of the maximum response obtained to a
reference agonist, carbachol (10 μM).
- 15 Calculations: The averages of the triplicate LTD₄
concentration-response curves both in the presence and
absence of the test compound were plotted on log graph
paper. The concentration of LTD₄ needed to elicit
30% of the contraction elicited by carbachol was
20 measured and defined as the EC₃₀. The pA₂ value
for the test compound was determined by the following
equations:
1.
$$\frac{EC_{30} \text{ (presence of test compound)}}{EC_{30} \text{ (presence of vehicle control)}} = \text{dose ratio} = X$$
 - 25 2. $K_B = \text{concentration of test compound} / (X-1)$
 3. $pA_2 \cong -\log K_B$

In vivo: Anesthetized, spontaneously breathing guinea
30 pigs (Adult male albino Hartley strain) were monitored on
a Buxco pulmonary mechanics computer. Changes in airway
resistance (R_L) were calculated by the computer on a
breath-by-breath basis at isovolumic points from signals
measuring airflow and transpulmonary pressure using
35 differential pressure transducers. Animals received
either test compound or vehicle control intravenously via

1 the jugular vein. LTD₄ was then injected into the
jugular vein. The bronchoconstriction produced was
reflected by % changes in airways resistance relative to
the baseline values obtained prior to injection of the
5 test compound or vehicle control. Each guinea pig
received either vehicle control or test compound.

Calculations: The average of 3 - 6 animals per
treatment was calculated using the % changes in the
pulmonary parameters for control and test
10 compound-treated animals. The average % inhibition by
the test compound was calculated from the following
equation:

$$15 \quad \frac{\frac{R_L}{(\text{vehicle control})} - \frac{R_L}{(\text{test compound})}}{\frac{R_L}{(\text{vehicle control})}} \times 100$$

The compounds of this invention possess
biosignificant antagonist activity against leukotrienes,
primarily leukotriene D₄. Representative of the
20 antagonist activity of the compounds of this invention,
tabulated below are a number of claimed compounds and the
pA₂ values and the R_L values calculated from the above
test protocols.

25 <u>Compounds of the Formula (II)</u>					<u>In Vitro</u>
					<u>pA₂</u>
<u>X</u>	<u>m</u>	<u>R₁</u>	<u>R₂</u>		
-CO ₂ H	1	-H	-OH	6.0	
30 -CH ₂ OH	1	-H	-OH	5.3	
-CHCH ₂ OH OH	1	-H	-OH	5.2	

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1 The specificity of the antagonist activity of a
number of the compounds of this invention is demonstrated
by relatively low levels of antagonism toward agonists
such as potassium chloride, carbachol, histamine and
5 PGF_{2α}.

Pharmaceutical compositions of the present invention
comprise a pharmaceutical carrier or diluent and an
amount of a compound of the formula (I) or a pharmaceutically
acceptable salt, such as an alkali metal salt
10 thereof sufficient to produce the inhibition of the
effects of leukotrienes, such as symptoms of asthma and
other allergic diseases.

When the pharmaceutical composition is employed
in the form of a solution or suspension, examples of
15 appropriate pharmaceutical carriers or diluents include:
for aqueous systems, water; for non-aqueous systems,
ethanol, glycerin, propylene glycol, corn oil, cottonseed
oil, peanut oil, sesame oil, liquid parafins and mixtures
thereof with water; for solid systems, lactose, kaolin and
20 mannitol; and for aerosol systems, dichlorodifluoromethane,
chlorotrifluoroethane and compressed carbon dioxide. Also,
in addition to the pharmaceutical carrier or diluent, the
instant compositions may include other ingredients such as
stabilizers, antioxidants,
25 preservatives, lubricants, suspending agents, viscosity
modifiers and the like, provided that the additional
ingredients do not have a detrimental effect on the
therapeutic action of the instant compositions.

The nature of the composition and the
30 pharmaceutical carrier or diluent will, of course, depend
upon the intended route of administration, i.e.
parenterally or by inhalation.

In general, particularly for the prophylactic
treatment of asthma, the compositions will be in a form
35 suitable for administration by inhalation. Thus the
compositions will comprise a suspension or solution of the

1 active ingredient in water for administration by means of
a conventional nebulizer. Alternatively the compositions
will comprise a suspension or solution of the active
ingredient in a conventional liquified propellant or
5 compressed gas to be administered from a pressurized
aerosol container. The compositions may also comprise the
solid active ingredient diluted with a solid diluent for
administration from a powder inhalation device. In the
above compositions, the amount of carrier or diluent will
10 vary but preferably will be the major proportion of a
suspension or solution of the active ingredient. When the
diluent is a solid it may be present in less, equal or
greater amounts than the solid active ingredient.

For parenteral administration the pharmaceutical
15 composition will be in the form of a sterile injectable
liquid such as an ampul or an aqueous or nonaqueous liquid
suspension.

Usually a compound of formula I is administered
to an animal subject in a composition comprising a
20 nontoxic amount sufficient to produce an inhibition of the
symptoms of an allergic response. When employed in this
manner, the dosage of the composition is selected from the
range of from 350 mg to 700 mg of active ingredient for
each administration. For convenience, equal doses will be
25 administered 1 to 4 times daily with the daily dosage
regimen being selected from about 350 mg to about 2800 mg.

The pharmaceutical preparations thus described
are made following the conventional techniques of the
pharmaceutical chemist as appropriate to the desired end
30 product.

Included within the scope of this disclosure is
the method of inhibiting the symptoms of an allergic
response resulting from a mediator release which comprises
administering to an animal subject a therapeutically
35 effective amount for producing said inhibition of a
compound of formula I, preferably in the form of a

1 pharmaceutical composition. The administration may be
carried out in dosage units at suitable intervals or in
single doses as needed. Usually this method will be
practiced when relief of allergic symptoms is specifically
5 required, however, the method is also usefully carried out
as continuous or prophylactic treatment. It is within the
skill of the art to determine by routine experimentation
the effective dosage to be administered from the dose
range set forth above, taking into consideration such
10 factors as the degree of severity of the allergic
condition being treated, and so forth.

The following examples illustrate the preparation
of the compounds of this invention and their incorporation
into pharmaceutical compositions and as such are not to be
15 considered as limiting the invention set forth in the
claims appended hereto.

EXAMPLE 1

Preparation of 3-[(2-carboxyethyl)thio]-4(Z)-
heptadecen-1,2-diol

- 20 (a) Heptadec-2(E),4(Z)-dienyl tetrahydropyranyl ether
1(a)(1)
Heptadec-2(E),4(E)-dienyl tetrahydropyranyl ether
1(a)(2)

Tridecyltriphenyl phosphonium bromide (189 g, 0.3
25 mole) was dissolved in 900 ml of tetrahydrofuran and
cooled to 0° in an ice-salt bath while stirring under
argon. A 2.2 N solution of n-butyllithium in hexane (250
ml, 0.36 mole) was added dropwise over a period of 30
minutes. The mixture was stirred for an additional 20
30 minutes and then cooled to -70° in a dry ice-acetone
bath. The 4-hydroxybut-2(E)-ene-1-al tetrahydropyranyl
ether (51 g, 0.3 mole in 225 ml of tetrahydrofuran was
added dropwise over a period of 35 minutes and the mixture
stirred for an additional hour at -70°. The mixture was
35 then poured into 6.25 liters of ether and stirred for 20
minutes. The resulting mixture was filtered through glass

1 fiber filter paper. The filtrate was evaporated and the residue triturated with hexane, filtered and evaporated to give a 3:1 mixture of 1(a)(1): 1(a)(2).

(b) Heptadec-2(E),4(Z)-dien-1-ol 1(b)(1)

5 Heptadec-2(E),4(E)-dien-1-ol 1(b)(2)

The mixture of compounds 1(a)(1) and 1(a)(2) (80 g, 0.24 mole) was dissolved in 3 liters of methanol and the pyridinium p-toluenesulfonic acid (3 g, 0.012 mole) was added to the mixture stirring under argon at room temperature. The progress at the reaction was monitored by tlc. When the reaction was complete the solvent was evaporated and the residue flash chromatographed on 500 grams of silica gel eluted with 10% ethyl acetate in hexane to give a 3:1 mixture of 1(b)(1):1(b)(2).

15 Separation of 1(b)(1) from 1(b)(2) was accomplished by careful chromatography on silica gel. Compound 1(b)(1) mp 34°-37°. Compound 1(b)(2) mp 51-55°.

(c) Trans-2,3-epoxy-heptadec-4-Z-ene-1-ol 1(c)

Compound 1(b)(1) (2.52 g, 10 mmol) was dissolved in 100 ml of methylene chloride stirring at room temperature under argon. A 0.5 N solution of sodium bicarbonate (30 ml) was added. The 85% m-chloroperbenzoic acid (2.03 g, 10 mmol) was added slowly in small portions. The mixture was stirred for 1.5 hours after the addition was complete. The phases were separated and the aqueous phase washed with methylene chloride. The combined organic phases were dried over anhydrous sodium sulfate filtered and evaporated. The residue was flash chromatographed on 100 grams of silica gel eluted with 10-20% ethyl acetate-hexane to give compound 1(c).

(d) 3-[(2-Carbomethoxyethyl)thio]-4(Z)-heptadecen-1,2-diol 1(d)

Compound 1(c) (7.2 g, 26.9 mmol) was dissolved in 40.2 ml of methanol containing 2% triethylamine. This solution was stirred at room temperature under argon and a solution of methyl-3-mercaptopropionate (4.92 ml, 44.4

1 mmol) and triethylamine (11.16 ml, 80.2 mmol) in 40.2 ml
of methanol was added dropwise over a period of 15
minutes. The mixture was stirred for 5 hours at room
temperature and then placed in the refrigerator
5 overnight. The solvents were evaporated and the residue
flash chromatographed on 500 grams of silica gel eluted
with 10-50%, ethyl acetate in hexane to give compound
1(d), mp. 33-36°.

(e) 3-[(2-Carboxyethyl)thio]-4(Z)-heptadecen-1,2-diol 1(e)

10 Compound 1(d) (500 mg, 1.29 mmol) was dissolved
in 2 ml of methanol and stirred under argon. A 1N
solution of sodium hydroxide (0.65 ml, 0.65 mmol) was
added dropwise and the mixture stirred for 0.5 hours at
room temperature. An addition of 0.65 ml of a 1N NaOH
15 solution was added and the mixture stirred for 1 hour.
TLC indicated that some starting material still remained
so an additional 0.2 ml of a 1N NaOH solution was added
and the mixture stirred for an additional 1.5 hours. The
methanol was stripped off and the residue acidified with
20 dilute hydrochloric acid. The mixture was extracted with
diethyl ether and the organic phase dried with anhydrous
magnesium sulfate, filtered, and evaporated to give crude
product. This was recrystallized from diethyl ether-
hexane to give the desired compound, mp 76-77°.

25		Theory	Found
	C	64.13	64.39
	H	10.23	10.22
	S	8.56	8.78

EXAMPLE 2

30 Preparation of 2-[(2-carboxyethyl)thio]-3(Z)-hexa-
decen-1-ol

(a) 2-[(2-Carbomethoxyethyl)thio]-3(Z)-hexadecen-1-al 2(a)

Compound 1(d) (2 g, 5.15 mmol) was dissolved in
10 ml of diethyl ether and stirred in a room temperature
35 water bath. A saturated solution (100 ml) of periodic
acid in diethyl ether was added in a single portion. The

- 1 resulting mixture was stirred for two minutes and then immediately flash chromatographed on 150 g of silica gel with 10% ethyl acetate in hexane to give compound 2(a).
 (b) 2-[(2-Carbomethoxyethyl)thio]-3(Z)-hexadecen-1-ol
 5 Compound from Example 2(a) (192 mg, 0.5 mmol) was dissolved in 1 ml of methanol and stirred at 0° under argon. Sodium borohydride (38 mg, 1 mmol) was added and the mixture stirred at 0° for 5 minutes. The mixture was acidified with dilute hydrochloric acid and evaporated.
 10 The residue was taken up in diethyl ether and washed with dilute hydrochloric acid, aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and evaporated to give crude product which was flash chromatographed on 20 grams of silica gel eluted with 15%
 15 ethyl acetate in hexane to give the above-noted compound.
 (c) 2-[(2-Carboxyethyl)thio]-3(Z)-hexadecen-1-ol
 Compound from Example 2(b) (180 mg, 0.5 mmol) was dissolved in 1 ml of methanol and a 1N solution of sodium hydroxide (1 ml, 1 mmol) was added. The mixture was
 20 stirred at room temperature under argon for 3 hours and then placed in the freezer over the weekend after which time it was stirred for an additional 2 hours at room temperature until tlc indicated only a trace of starting material remained. The methanol was stripped off and the
 25 residue acidified with dilute hydrochloric acid and extracted with chloroform. The organic phase dried over anhydrous magnesium sulfate filtered and evaporated to give crude product. This was recrystallized from hexane at -78°C to give the desired compound, mp 39°-40°.

30		Theory	Found
	C	66.23	66.47
	H	10.53	10.77
	S	9.30	9.15

EXAMPLE 3

1

Preparation of 2-[(2-carboxyethyl)thio]-3(Z)-hexadecenoic acid

5

(a) 2-[(2-Carbomethoxyethyl)thio]-3(Z)-hexadecenoic acid
3(a)(1)
Methyl-2-[(2-carbomethoxyethyl)thio]-3(Z)-hexadecenoate 3(a)(2)

Compound from Example 2(a) (0.8 g, 2.25 mmol) was dissolved in 5.5 ml of acetone. The solution was cooled to -40°C. and stirred under argon. Jones reagent (0.3 ml, 0.6 mmol) was added and the mixture stirred between -30° and -40°C for 30 minutes. Additional Jones reagent (0.3 ml, 0.6 mmol) was added and the mixture stirred for 1 hour. The remaining Jones reagent (0.145 ml, 0.29 mmol) was added. Thirty minutes later the reaction which had been maintained in a temperature range of -30° to -40°C throughout the reaction was quenched by the addition of 1 ml of isopropanol. The solvents were stripped off and the residue partitioned between diethyl ether and H₂O. The aqueous phase was extracted with diethyl ether. The combined organic phases were dried over anhydrous MgSO₄ filtered and evaporated to give the crude product 3(a)(1). In order to facilitate purification, compound 3(a)(1) was treated with excess diazomethane in diethyl ether at 0° and allowed to warm to room temperature. The solvents were evaporated and the residue flash chromatographed on 200 grams of silica gel eluted with 5% EtOAc-hexane to give the desired product 3(a)(2).

(b) 2-[(2-Carboxyethyl)thio]-3(Z)-hexadecenoic acid

Compound 3(a)(2) (0.16 g, 0.41 mmol) was dissolved in 3.2 ml of methanol and stirred under argon at 0°C. A 1N solution of sodium hydroxide (1.6 ml, 1.6 mmol) was added and the ice bath removed. The mixture was stirred at room temperature for 2 1/2 hours. The methanol was evaporated and the residue cooled in an ice bath and acidified with dilute HCl. The aqueous phase was

1 extracted twice with diethyl ether. The combined ether
extracts were dried over anhydrous sodium sulfate,
filtered and evaporated to give crude product. This was
recrystallized from diethyl ether-hexane to give the
5 desired compound, mp 52-54°C. Anal. Calcd. C: 63.65; H:
9.56; S: 8.94; Found C: 63.59; H: 9.45; S: 9.24.

EXAMPLE 4

Preparation of 5-[(2-amino-3-carboxymethylamino-3-oxopropyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid as the
10 4(R),5(S) isomer, 4(S),5(R) isomer and the mixture of the
two isomers.

(a) 3-Carbomethoxypropionyl chloride 4(a)

To an ice-cold solution of mono-methyl succinate,
(150 g, 1.135 mol) in 900 ml of methylene chloride and 3
15 ml of N,N-dimethylformamide was added 119 ml (1.26 mol) of
oxalyl chloride, while keeping the pot temperature below
5°C. After the addition was complete, the reaction
mixture was stirred at 0°C for 1 hour and then
concentrated in vacuo to give a crude yellow liquid, which
20 was used without purification in the Rosenmund reduction.

(b) 3-Carbomethoxypropionaldehyde 4(b)

To the acid chloride, 4(a) (8.9 g, 0.059 mol) in
200 ml of sieve-dried tetrahydrofuran was added 6.9 ml
(0.059 mol) of 2,6-lutidine. After standing at room
25 temperature for 30 minutes, the mixture was filtered and
0.7 g of 10% palladium on carbon was added to the
filtrate. The mixture was hydrogenated at 50 psi for 2
hours, the solids were filtered off and the filtrate
concentrated. The residue was dissolved in methylene
30 chloride, washed twice with 10% hydrochloric acid solution
and then twice with 5% sodium bicarbonate solution. The
organic extract was dried with anhydrous sodium sulfate
and concentrated in vacuo. Kugelrohr distillation
(40-55°C/.05 mm) yielded a colorless liquid.

1 (c) 5-Carbomethoxy-2-pentenal 4(c)

 To a mechanically-stirred solution of 4(b) (72.1 g, 0.620 mol) in 750 ml of toluene under argon was added 235.9 g (0.776 mol) of formylmethylene triphenyl-phosphorane. The reaction mixture was refluxed for 1.5 hours, cooled to room temperature and then concentrated in vacuo. The residue was left standing under diethyl ether at 0°C overnight. The mixture was filtered and the solid was washed with cold ether. The filtrate was concentrated and the resulting maroon oil was subjected to Kugelrohr distillation. The product was collected at 65-80°C/.05 mm.

10 (d) Methyl 4,5-Epoxy-6-oxohexanoate 4(d)

 To a solution of 36.4 ml of a 30% hydrogen peroxide solution and 58.2 ml of 1N sodium bicarbonate in 800 ml of methanol and 400 ml of water under argon was added dropwise over 45 minutes 41.2 g (0.29 mol) of 4(c) in 400 ml of methanol. After the addition was complete, the reaction was stirred for 2.5 hours at room temperature, while maintaining the pH between 9 and 9.5 by the addition of sodium bicarbonate solution. The reaction mixture was then poured into one liter of saturated ammonium sulfate solution, the methanol was removed in vacuo, the solids were filtered off and the product was extracted into methylene chloride. The aqueous layer was back extracted twice, the combined extracts were dried with anhydrous sodium sulfate and then concentrated to give a crude golden oil. The product was Kugelrohr distilled at 82-9°C/0.1 mm.

15 (e) Methyl 4,5-epoxy-6(Z)-nonadecenoate 4(e)

 To an ice-cold solution of tridecyl triphenyl-phosphonium bromide (preparation described below) (97.2 g, 0.185 mol) in 600 ml of sieve-dried tetrahydrofuran under argon was added dropwise 17.1 ml of a 2.4 M solution of n-butyl lithium in hexane; the temperature was maintained at 0°C during the 30 minute addition. The reaction mixture was stirred at this temperature for an additional

20 (f) Methyl 4,5-epoxy-6(Z)-nonadecenoate 4(f)

25 (g) Methyl 4,5-epoxy-6(Z)-nonadecenoate 4(g)

30 (h) Methyl 4,5-epoxy-6(Z)-nonadecenoate 4(h)

35 (i) Methyl 4,5-epoxy-6(Z)-nonadecenoate 4(i)

1 15 minutes, cooled to -78°C (dry ice/isopropanol) and then
26.5 g (0.168 mol) of 4(d) in 150 ml of dried tetrahydro-
furan was added dropwise over 30 minutes. After the
addition was complete, the reaction was stirred for 1 hour
5 at -78°C and then concentrated in vacuo at 24°C. The
residue was triturated with hexane and then left standing
at 0°C overnight. The hexane was decanted and then the
residue was sonicated four times with hexane. The
combined extracts were concentrated in vacuo and the crude
10 product purified by preparative HPLC (2 Waters Prepak
silica columns, eluting with 8% ethyl acetate in hexane),
giving 4(e) as an oil.

(f) Tridecyl triphenyl phosphonium bromide

A solution of 1-bromotridecane (100 g, 0.4 mol)
15 and triphenyl phosphine (100 g, 0.4 mol) in 500 ml of
xylenes was refluxed overnight. The reaction mixture was
then cooled to room temperature and poured into diethyl
ether. The resulting oil was washed three times with
ether, dissolved in methylene chloride and then
20 concentrated in vacuo. The oil was left standing in
diethyl ether at 0°C overnight and then concentrated in
vacuo to give a white solid.

(g) 4-Hydroxy-5-[(2-trifluoroacetamido-3-carbomethoxy-
methylamino-3-oxopropyl)thio]-6(Z)-nonadecenoic acid,
25 γ -lactone and methyl ester

To the epoxide, 4(e) (12.9 g, 0.04 mol) under
argon at room temperature was added dropwise over 1 hour a
solution of 14.5 g (0.05 mol) of 2-trifluoroacetamido-3-
carbomethoxymethylamino-3-oxopropylmercaptan

30
$$\begin{array}{c} \text{O} \\ \parallel \\ \text{F}_3\text{C}-\text{C}-\text{NH} \\ | \\ \text{O} \\ \parallel \end{array}$$

(HSCH₂CHC(=O)NHCH₂CO₂CH₃) in triethylamine (6.7 ml)/methanol
(150 ml). The reaction mixture was stirred at room
temperature overnight and then concentrated in vacuo. The
35 residue was dissolved in a minimum volume of methylene
chloride, 100 ml. of hexane was added and then this

1 solution was stored at -15°C for 1 hour. The resulting
solid was filtered off and then the filtrate was
concentrated in vacuo, to give a crude oil, consisting of
a mixture of the desired products.

5 (h) 4(R)-Hydroxy-5(S)-[(2-trifluoroacetamido-3-carbo-
methoxymethylamino-3-oxopropyl)thio]-6(Z)-nonadecenoic
acid γ -lactone and 4(S)-Hydroxy-5(R)-[(2-trifluoro-
acetamido-3-carbomethoxymethylamino-3-oxopropyl)-
thio]-6(Z)-nonadecenoic acid, γ -lactone

10 The crude mixture from Example 4(g) (20.4 g.) in
200 ml of toluene was heated to 80°C in the presence of 75
mg of p-toluenesulfonic acid for 15 minutes. The reaction
mixture was then concentrated in vacuo and the resulting
crude oil was purified by preparative HPLC (2 Waters
15 Prepak silica columns, eluting with 45% ethyl acetate in
hexane) to give the desired products as the pure 4(R),
5(S) isomer and the pure 4(S), 5(R) isomer.

(i) 4(R)-Hydroxy-5(S)-[(2-amino-3-carboxymethylamino-3-oxo-
propyl)thio]-6(Z)-nonadecenoic acid, hydrate

20 The lactone of Example 4(h) in the 4(R), 5(S)
isomer form, (1.9 g, 0.00327 mol) in aqueous sodium
hydroxide (0.72 g, 0.018 mol in 50 ml water) was stirred
at room temperature overnight. The pH of the reaction
mixture was then adjusted to 3.5 with concentrated
25 hydrochloric acid and the resulting solid was collected
and dried: mp 144-146°C; Anal. Calcd. for
 $C_{24}H_{44}N_2O_6S \cdot 1 \frac{1}{4} H_2O$: C, 56.38; H, 9.17; N,
5.48. Found: C, 56.16; H, 8.83; N, 5.54.

Similarly, the lactone of Example 1(h) in the
30 4(S), 5(R) isomer form was converted to the desired 4(S),
5(R) isomer of the above noted compound: mp 141-143°C;
Anal. Calcd. for $C_{24}H_{44}N_2O_6S \cdot 1 \frac{1}{4} H_2O$: C, 56.39;
H, 9.17; N, 5.48; Found: C, 56.20; H, 8.88; N, 5.18.

The isomeric mixture of the desired product was
35 obtained treating the mixture of products prepared
according to Example 1(g) without separation as described

- 1 above: mp 140-143°C; Anal. Calcd for $C_{24}H_{44}N_2O_6S \cdot 1 \frac{1}{4} H_2O$: C, 56.39; H, 9.17; N, 5.48; Found: C, 56.44; H, 8.75; N, 5.16.

EXAMPLE 5

- 5 Preparation of 4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-nonadecenoic acid as a mixture of the 4(R),5(S) and the 4(S),5(R) isomers.

- A solution of 1.32 g (4.1 mmol) of 4,5-epoxy-6(Z)-nonadecenoic acid methyl ester and 1.46 g (12.2 mmol) of methyl-3-mercaptopropionate in 20 ml of methanol was treated with 1.62 g (16.1 mmol) of triethylamine in 10 ml of methanol under an argon atmosphere overnight. The reaction mixture was concentrated in vacuo and purification was carried out by chromatography on silica gel with hexane/ether (60/40) to give diester which contained some mono ester/lactone as evidenced by IR and tlc (CH_2Cl_2 /hexane/acetone, 47/47/5).

- A solution of this diester/lactone mixture (1.6 g, 3.6 mmol) in 30 ml of methanol was treated overnight with 1.43 g (36 mmol) of sodium hydroxide in 5 ml of water at room temperature, under an argon atmosphere. The reaction mixture was partly concentrated in vacuo, redissolved in 20 ml of water, and acidified with dilute phosphoric acid. The aqueous solution was extracted 3 times with 50 ml of ether, and the extracts were dried over magnesium sulfate, filtered and concentrated in vacuo to give white crystalline solid; m.p. 78-80°C,. Anal. calcd. for $C_{22}H_{40}O_5S$: C, 63.43, H, 9.68. Found: C, 63.11, H, 9.69.

EXAMPLE 6

- 30 Preparation of 5-[(3-carboxymethylamino-3-oxo-propyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid

- The above named compound was prepared by the general method of Example 5 using 3-carboxymethylamino-3-oxopropyl mercaptan, which in turn was prepared by the coupling reaction between 3,3'-dithio-dipropionic acid and

- 1 glycine methyl ester using DCC, followed by the reduction
of the disulfide with tri-n-octyl phosphine in
acetone/water 1:1 mixture. Product was obtained as an
oil. Anal. calcd. for $C_{24}H_{43}NO_6S$: C, 60.85;
5 H, 9.15, N, 2.95. Found: C, 60.65; H, 9.07; N, 2.89.

EXAMPLE 7

Preparation of 5-[(3-carboxymethyl-N-methylamino-
3-oxopropyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid

- The above named compound was prepared by the
10 general method of Example 5 using 3-carboxymethyl-
N-methylamino-3-oxopropyl mercaptan. Mercaptan was
prepared by coupling reaction between p-methoxy
benzylthiopropionic acid and N-methyl glycine methyl ester
in the presence of DCC, followed by treatment with HF at
15 -78°C. Product obtained had a melting point of 80-82°C.
Anal. calcd.: C, 61.57; H, 9.30; N, 2.87. Found: C,
61.55, H, 9.65; N, 3.02.

EXAMPLE 8

- Preparation of 5-[(carboxymethyl)thio]-4-hydroxy-
20 6(Z)-nonadecenoic acid

The above named compound was prepared by the
general method of Example 5 using commercial methyl
thioglycolate: mp 50-52°C. Anal. calcd. for
 $C_{21}H_{38}O_5S$: C, 62.65; H, 9.51. Found: C, 62.74; H,
25 9.57.

EXAMPLE 9

Preparation of 5-[(3-carboxypropyl)thio]-4-
hydroxy-6(Z)-nonadecenoic acid

- The above named compound was prepared by the
30 general method of Example 5 using commercial 4-mercapto-
butyric acid, mp 56-58°C. Anal. calcd. for
 $C_{23}H_{42}O_5S \cdot 1/4 H_2O$: C, 63.48; H, 9.96. Found:
C, 63.29; H, 9.75.

1

EXAMPLE 10

Preparation of 5-[[2-(aminocarbonyl)ethyl]thio]-4-hydroxy-6(Z)-nonadecenoic acid

- 5 The above named compound was prepared by the general method of Example 5 using 2-(aminocarbonyl)ethyl mercaptan. Mercaptan was prepared by treatment of 3,3'-dithiodipropionyl iodide with concentrated ammonium hydroxide followed by the reduction of disulfide with tri-n-octylphosphine and acetone/water 1:1 mixture.
- 10 Product obtained had a melting point of 84-86°C. Anal. calcd. for $C_{22}H_{41}NO_4S$: C, 63.57; H, 9.94. Found: C, 63.56; H, 9.82.

EXAMPLE 11

- Preparation of 4-hydroxy-5-[(2-amino-2-carboxy-ethyl)thio]-6(Z)-nonadecenoic acid as the 4(R),5(S) isomer and the 4(R),5(S) isomer

- (a) 4-Hydroxy-5-[(2-trifluoroacetamido-2-carbomethoxy-ethyl)thio]-6(Z)-nonadecenoic acid, methyl ester and γ -lactone
- 20 To the epoxide, methyl-4,5-epoxy-6(Z)-nonadecenoate (4e) (0.9 g, 0.00277 mol) under argon at room temperature was added dropwise a solution of 1.2 g (0.00519 mol) of 2-trifluoroacetamido-2-carbomethoxy-ethylmercaptan in triethylamine (0.88 ml)/methanol (15
- 25 ml). The reaction mixture was stirred at room temperature for 30 hours, concentrated in vacuo and then filtered through a silica gel bed, eluting the product mixture with chloroform. The chloroform wash was concentrated to give a mixture of the above-noted methyl ester and γ -lactone.
- 30 (b) 4-Hydroxy-5-[(2-trifluoroacetamido-2-carbomethoxy-ethyl)thio]-6(Z)-nonadecenoic acid, γ -lactone

- The crude mixture (2 g) of the methyl ester and γ -lactone from Example 11(a) in 75 ml of toluene was heated to 80°C in the presence of 27 mg of
- 35 p-toluenesulfonic acid for 20 minutes. The reaction mixture was then concentrated in vacuo and the residue was

- 1 taken up in methylene chloride, washed with 5% sodium
bicarbonate solution, dried with brine and anhydrous
sodium sulfate and then concentrated in vacuo. The
resulting crude oil was applied to the Water's Preparative
5 HPLC (2 Prepak silica columns, eluting with 25% ethyl
acetate in hexane) to give the desired products as the
4(R),5(S) isomer and the 4(S),5(R) isomer. Each
individual diastereomer was purified further on a silica
"flash" column, eluting with 30% ethyl acetate in hexane.
- 10 (c) 4(R)-Hydroxy-5(S)-[(2-amino-2-carboxyethyl)thio]-6(Z)-
nonadecenoic acid, sodium salt

A partial suspension of 4(R),5(S) isomer of the
γ-lactone of Example 11(b) (0.3 g, 0.00057 mol) in aqueous
sodium hydroxide (0.205 g, 0.004 mol in 13 ml water) was
15 stirred for 24 hours at room temperature. The pH of the
reaction mixture was then adjusted to 3.5 with
concentrated hydrochloric acid to give the desired
product: mp 168-170°C. Anal. calcd. for C₂₂H₄₁NO₅S
1Na (-1H): C, 58.12; H, 8.87; N, 3.08. Found: C, 57.99;
20 H, 8.85; N, 3.70.

- (d) 4(S)-Hydroxy-5(R)-[(2-amino-2-carboxyethyl)thio]-6(Z)-
nonadecenoic acid, sodium salt
- The reaction was carried out as described in
Example 11(c), to give the desired product: mp 159-161°C.
- 25 Anal. Calcd. for C₂₂H₄₁NO₅S· 1.5 Na (-1.5 H):
C, 56.69; H, 8.54; N, 3.01. Found: C, 56.40; H, 8.19; N,
3.33.

EXAMPLE 12

- Preparation of 5[-(2-amino-3-carboxamidomethyl-
30 amino-3-oxopropyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid
- (a) 4(R)-Hydroxy-5(S)-[(2-trifluoroacetamido-3-carbamoyl-
methylamino-3-oxopropyl)thio]-6(Z)-nonadecenoic acid,
γ-lactone-4(R)-hydroxy-5(S)-[(2-trifluoroace' amido-3-
carbamoylmethylamino-3-oxopropyl)thio]-6(Z)-nonadecen-
35 amide

A mixture of lactone methyl ester prepared
according to Example 4(g) (0.41 g, 0.7 mmol) in 10 ml of

1 dimethoxyethane, 10 ml of methanol, and 20 ml of
concentrated ammonium hydroxide solution was stirred at
0°C for 2 hours. The mixture was neutralized in the cold
with concentrated hydrochloric acid to pH 7.5. The crude
5 product was partitioned into methylene chloride. The
aqueous phase was further extracted 2 x 40 ml methylene
chloride. The combined extracts were washed with
saturated sodium chloride solution, dried over sodium
sulfate, and evaporated to give oil residue. Flash column
10 chromatography (silica gel, 1.5" x 6", 3% CH₃OH/CHCl₃,
25 ml fraction) gave the desired products. The
6(Z)-nonadecenamide had the following properties: mp
143-5°C; Anal. calcd. for C₂₆H₄₅F₃N₄O₅S: C,
53.59; H, 7.78; N, 9.61. Found: C, 53.86; H, 7.52; N,
15 9.83.

(b) 4(R)-Hydroxy-5(S)-[(2-amino-3-carbamoylmethylamino-
3-oxopropylthio]-6(Z)-nonadecenoic acid

A mixture of 120 mg (0.2 mmol) of the γ-lactone
of Example 12(a) in 5 ml of 0.2 M sodium hydroxide
20 solution was stirred at room temperature for 18 hours.
The mixture was acidified to pH 3 by adding a concentrated
hydrochloric acid solution in ice-bath. The resulting
precipitates were filtered and washed quickly with cold
water and dried at 56°C for 24 hours to give the desired
25 product, mp. 143 -5°C; Anal. calcd.: C, 57.51; H, 9.35;
N, 8.38; Found C, 57.50; H, 9.42; N, 6.72.

EXAMPLE 13

Preparation of 3-hydroxy-4-[(2-carboxyethyl)thio]-
5(Z)-octadecenoic acid

30 (a) Methyl 3-(1,2-dihydroxyheptadec-4(Z)-enyl)thio-
propionate 13(a)

Compound 1(c) (7.2 g, 26.9 mmol) was dissolved in
40.2 ml of methanol containing 2% triethylamine. This
solution was stirred at room temperature under argon and a
35 solution of methyl 3-mercaptopropionate (4.92 ml, 44.4
mmol) and triethylamine (11.16 ml, 80.2 mmol) in 40.2 ml

1 of methanol was added dropwise over a period of 15
minutes. The mixture was stirred for 5 hours at room
temperature and then placed in the refrigerator
overnight. The solvents were evaporated and the residue
5 flash chromatographed on 500 grams of silica gel eluted
with 10-50% ethyl acetate in hexane to give compound
13(a), mp. 33-36°.

(b) 2-[(2-Carbomethoxyethyl)thio]hexadec-3(Z)-enal 13(b)

Compound 13(a) (2 g, 5.15 mmol) was dissolved in
10 10 ml of diethyl ether and stirred in a room temperature
water bath. A saturated solution (100 ml) of periodic
acid in diethyl ether was added in a single portion. The
resulting mixture was stirred for two minutes and then
immediately flash chromatographed on 150 g of silica gel
15 with 10% ethyl acetate in hexane to give compound 13(b).

(c) Methyl 3-hydroxy-4-[(2-carbomethoxyethyl)thio]octadec-
5(Z)-enoate 13(c)

A dry flask sealed with a septum and maintained
under an argon atmosphere was charged with 4.5 ml of
20 hexane and cooled in an ice bath. A 2.2 M solution of
n-BuLi (1.03 ml, 2.25 mmol) was added followed by the
dropwise addition of diisopropyl amine (0.315 ml, 2.25
mmol). The solution was stirred at 0°C for 10 minutes and
then cooled to -78°C in a dry ice-acetone bath for 15
25 minutes. A solution of methyl acetate (0.18 ml, 2.25
mmol) in 1.5 ml hexane was added over a period of 1 minute
and the mixture stirred at -78°C for an additional
minute. The mixture at this time was almost clear.

Compound 13(b) (750 mg, 2.1 mmol) in 1.5 ml of hexane was
30 added over a period of 1 minute resulting in a clear
yellow solution which was stirred at -78°C for an
additional 15 minutes. The reaction mixture was then
flash chromatographed on 100 grams of silica gel eluted
with 15% ethyl acetate in hexane to give compound 13(c).

1 (d) 3-Hydroxy-4-[(2-carboxyethyl)thio]-5(Z)-octadecenoic acid

Compound 13(c) (0.2 g, 0.46 mmol) was dissolved in 5 ml of methanol and stirred under an argon atmosphere at 0°C. A 1N solution of sodium hydroxide (2 ml, 2 mmol) was added dropwise over a period of 0.5 minute. The ice bath was removed and the reaction allowed to warm to room temperature for 2 hours. Most of the methanol was evaporated and the aqueous residue was cooled in an ice bath and acidified with dilute hydrochloric acid. The aqueous phase was extracted twice with diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to give crude product. This was recrystallized from diethyl ether-hexane to give the desired compound, mp 88-97°C. Anal. Calcd. C: 62.65; H: 9.51; S: 7.96; Found C: 62.32; H: 9.38; and S: 8.10.

EXAMPLE 14

Preparation of 5-[(2-carboxyethyl)thio]-6(Z)-nonadecenoic acid

20 (a) 2-Bromo-5-carbomethoxypentanoic acid 14(a)

To a solution of 30 gm (0.187 M) of 5-carbomethoxypentanoic acid in 250 ml of chloroform was added 90 gm of thionyl chloride. The mixture was refluxed for 2 hours, cooled and the solvent removed under vacuum. The residue was redissolved in 200 ml of carbon tetrachloride, 40 gm (0.225 M) of N-bromosuccinimide was added, the mixture heated to reflux, eight drops of a HBr/acetic acid mixture added, and the reaction refluxed for 3 hours. After cooling, the mixture was filtered and evaporated to dryness. The residue was dissolved in 250 ml of acetone to which was added dropwise 200 ml of a freshly prepared 5% sodium bicarbonate solution. After stirring for 15 minutes during which time the pH was constantly adjusted to pH 9 with sodium bicarbonate the mixture was acidified with dilute HCl, to a pH 1.0, concentrated in vacuo, and extracted with chloroform. The

1 organic phase was extracted with dilute bicarbonate solution, acidified and reextracted with chloroform. The extract was dried over MgSO_4 , filtered and evaporated to dryness to afford the desired compound as a viscous oil.

5 (b) 5-Carbomethoxy-2-[(methoxycarbonylpropyl)thio]-pentanoic acid 14(b)

A mixture of 42 gm (0.175 M) of 14(a), 50.68 g (0.42 M) of methyl-3-mercaptopropionate and 147 ml (1.05 M) of triethylamine in 250 ml of methanol was refluxed for 10 two hours, cooled and concentrated in vacuum. The residue was dissolved in ethyl acetate and extracted with 5% sodium bicarbonate. The aqueous extract was acidified with 3N HCl, extracted with chloroform, the extract dried over MgSO_4 , filtered and evaporated to dryness to afford 15 the desired compound.

(c) 5-Carbomethoxy-2-[(methoxycarbonylpropyl)thio]-pentanol 14(c)

A solution of 14(b) (40 g, 0.142 M) in THF (200 ml) was placed in a methanol-ice (-10°C) bath. The 20 contents were permitted to cool for 20 minutes at which time 12.57 g (0.156 M) of borane-methyl sulfide complex was added slowly over a period of 50 minutes, followed by refluxing for 30 minutes. Acetic acid (10 ml) was then added and excess THF evaporated. The reaction mixture was 25 dissolved in ethyl acetate (300 ml), washed with 5% sodium bicarbonate, dried over MgSO_4 and filtered. Evaporation afforded the crude alcohol.

(d) 5-Carbomethoxy-2-[(methoxycarbonylpropyl)thio]-pentanal 14(d)

30 Methylene chloride (10 ml.) and Me_2SO (1.78 g, 0.23 M) were combined and cooled to -65°C . TFAA (1.73 g, 0.015 M) was added dropwise to the cold solution, at which time a white precipitate formed. After 5 minutes at -65°C , a solution of 14(c) (2.0 g, 7.58 mmol) in 35 CH_2Cl_2 (5 ml) was added dropwise while maintaining the reaction mixture at -65°C . The mixture was then stirred

1 at -65°C for 30 minutes, followed by addition of TEA (2.30
g, 0.023 M) dropwise. A temperature below -60°C was
maintained until addition of TEA was complete. The bath
was then removed and the reaction permitted to warm to
5 room temperature. The mixture was diluted with
CH₂Cl₂, washed with 3N HCl, H₂O, twice with 5%
NaHCO₃ and once with brine. The organic phase was then
dried over MgSO₄, filtered and evaporated to dryness to
afford the crude aldehyde.

10 (e) Methyl-5-[(2-carbomethoxyethyl)thio]-6(Z)-non-
adecanoate 14(e)

A mixture of tridecyltriphenyl phosphonium
bromide (1.76 g, 3.35 M) and THF (20 ml) was permitted to
stir for 5 minutes at room temperature. The solution was
15 then cooled to -68°C and stirred for an additional 10
minutes. At which time n-butyllithium (3.05 mmol) was
slowly added while maintaining a -65°C temperature.
Following stirring for 10 minutes at -68°C the reaction
mixture was stirred for an additional 10 minutes at
20 -10°C. Upon recooling to -68°C, (0.918 g, 3.50 mmol) of
14(d) was dissolved in THF (10 ml) and slowly added. The
reaction was stirred for one hour at -68°C followed by
removal of the bath in order to warm the mixture to room
temperature. THF was then evaporated and the residue
25 dissolved in ethyl acetate, which was washed with 3N HCl,
water and twice with 5% NaHCO₃. The extract was dried
over MgSO₄, filtered and evaporated to dryness. The
product was flash chromatographed with 91% hexane: 9%
EtOAc to provide the nonadecanoate.

30 (f) 5-[(2-Carboxyethyl)thio]-6(Z)-nonadecanoic acid

Potassium carbonate (0.81 g, 5.84 mmol) was
dissolved in H₂O (10 ml), to which was added methanol
(5 ml). The solution was stirred for 2 minutes at room
temperature, followed by the addition of 14(e) (100 mg;
35 0.234 mmol) in MeOH (24 ml). The mixture was permitted to
stir overnight at room temperature, after which time

1 excess MeOH was evaporated and the remaining aqueous phase
was then washed with ethyl acetate, acidified to a pH =
1.0 with 3N HCl and extracted twice with ethyl acetate,
the extract was dried over MgSO_4 , filtered and
5 evaporated to an oil. The product was recrystallized from
ether-petroleum ether and cooled for one hour to afford
the nonadecanoic acid as a white crystalline solid (mp
53-54°C).

EXAMPLE 15

10 Preparation of 5-[(2-carboxyethyl)thio]-4-hydroxy-
6(Z)-nonadecenamide

The above named compound was prepared by
treatment of the compound of Example 5 with 1% solution of
trifluoroacetic anhydride in CH_2Cl_2 for 2 hours at
15 room temperature, followed by treatment with NH_3 in
methanol solution at 0°C for 0.5 hour and room temperature
overnight. Product was obtained as a crystalline solid mp
82-85°C; Anal. Calcd. for $\text{C}_{22}\text{H}_{41}\text{NO}_4\text{S}$ 0.3 M NH_3 :
C, 62.77; H, 9.89; N, 4.33. Found: C, 62.67, 62.98; H,
20 9.92, 9.78; N, 3.98, 4.00.

EXAMPLE 16

Preparation of 5-[(3-carboxymethylamino-3-
oxopropyl)thio]-4-hydroxy-6(Z)-nonadecenamide

A mixture of 0.9 g (1.4 mmol) of compounds of
25 Example 4(g) in 100 ml of 3.8% anhydrous ammonia in
ethanol solution was stirred at room temperature for 2
days. The reaction mixture was concentrated to dryness.
The residue was azeotroped with methylene chloride to give
0.9 g of off-white powder. The hygroscopic material was
30 dissolved in 10% NaOH solution (5 ml) and chromatographed
on a 3-cm-by-9-cm column of XAD-7 resin. After washing
with H_2O (100 ml), the column was eluted with aqueous
methanol solution (1:1) taking 20 ml per fraction.
Fraction 13 was collected to give the desired product as a
35 white amorphous powder, mp. 195-8°C. Anal Calcd. for
 $\text{C}_{24}\text{H}_{44}\text{N}_3\text{O}_5\text{S}$ Na(H) $2\text{H}_2\text{O}$: C, 52.82; H, 8.87; N,
7.70. Found: C, 52.65; H, 8.15; N, 7.72.

1

EXAMPLE 17

Preparation of 4-hydroxy-5-[(2-carboxyethyl)thio]-(Z)-hepadecenoic acid

5 The above named compound was prepared by the general method of Example 5 using 4,5-epoxy-6(Z)-heptadecenoic acid methyl ester, which was obtained by employing the general method of Example 4(e) using undecyltriphenyl phosphonium bromide. The product obtained had a melting point of 78.5-80°C. Anal. calcd.:
10 C, 61.82; H, 9.34; S, 8.25. Found C, 61.82; H, 9.10; S, 8.42.

EXAMPLE 18

Preparation of 4-Hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-heneicosenoic acid

15 The above named compound was prepared by the general method of Example 5 using 4,5-epoxy-6(Z)-heneicosenoic acid methyl ester, which was obtained by employing the general method of Example 4(e) using pentadecyltriphenyl phosphonium bromide. The product
20 obtained had a melting point 59-61°C. Anal calcd.: C, 64.82; H, 9.97; S, 7.21. Found C, 65.16; H, 10.07; S, 7.36.

EXAMPLE 19

Preparation of 4-[(2-carboxyethyl)thio]-5(Z)-octadecenoic acid
25

(a) Methyl-4-bromo-4-carboxybutanoate 19(a)

Methyl-4-(chloroformyl)butyrate (30.0 g, 0.182 M) was charged to a flask, along with 200 ml of CCl₄. To this solution N-bromosuccinimide (40.0 g, 0.219 M) was
30 added. The reaction mixture was heated to reflux and seven drops of 47% aqueous HBr was added, reflux conditions continued for approximately 2 hours. Following cooling to room temperature, the reaction was filtered and evaporated to dryness. The residue was then placed in the
35 refrigerator overnight. The residue was dissolved in 250 ml of acetone, to which is added saturated sodium

1 bicarbonate during which time the pH was adjusted to
 nine. With dilute HCl the mixture was then acidified to a
 pH = 1.0, concentrated and extracted with chloroform. The
 extract was dried over MgSO_4 , filtered and evaporated to
 5 dryness to afford the desired compound as an oil.

(b) Methyl-4-[(2-carbomethoxyethyl)thio]-4-carboxy
 butanoate 19(b)

To a stirred solution of 29.0 g (0.24 M) of
 methyl-3-mercaptopropionate and 61.0 g (0.60 M) of
 10 triethylamine in 200 ml of methanol was added 22.5
 (0.10 M) of 19(a) under argon. After stirring at room
 temperature for ten minutes, the reaction was heated to
 reflux for one and a half hours, cooled to room
 temperature and concentrated in a vacuum. The residue was
 15 then diluted with ethyl acetate, extracted with 5% sodium
 bicarbonate, acidified to pH 1.6 with dilute HCl and
 reextracted into chloroform several times. Organic
 extracts were then combined, dried over MgSO_4 , filtered
 and evaporated to dryness to afford the desired compound.

20 (c) Methyl-4-[(2-carbomethoxyethyl)thio]-5-hydroxy
 pentanoate 19(c)

A solution of 19(b) (21.4 g; 0.08 M) in THF
 (175 ml) was cooled to -10°C in a methanol-ice bath. The
 contents were permitted to cool for 10 minutes at which
 25 time borane methyl sulfide complex (7.2 g; 0.09 M) was
 added slowly. Following addition reaction was warmed to
 room temperature and then refluxed for approximately 15
 minutes. After cooling acetic acid (6 ml) was added and
 excess THF evaporated. The reaction mixture was
 30 dissolved in ethyl acetate, washed with 5% sodium
 bicarbonate, dried over MgSO_4 , filtered, evaporated to
 dryness to afford the crude alcohol. This material was
 then flash chromatographed using a 60% ethyl acetate in
 hexane system to yield a purer product.

1 (d) Methyl-4-[(2-carbomethoxyethyl)thio]-4-formyl
butanoate 19(d).

Methylene chloride (20 ml) and Me_2SO (1.14 ml; 0.016 M) were combined and cooled to -65°C . TFAA (0.91 ml; 0.012 M) was added dropwise to the cold solution at which time a white precipitate formed. After 5 minutes a solution of 19(c) (2.0 g; 0.008 M) in methylene chloride (3 ml) was added dropwise while maintaining the temperature at -65°C . The reaction mixture was then stirred for thirty minutes followed by addition of TEA (3.1 ml; 0.022 M) dropwise. The reaction mixture was stirred for an additional thirty minutes at -65°C , at which it was diluted with methylene chloride, washed with dilute HCl, water and then twice with 5% sodium bicarbonate. The organic phase was then dried over MgSO_4 , filtered and evaporated to dryness to afford the crude aldehyde. This material was flash chromatographed using 50% ethyl acetate in hexane resulting in purer product.

20 (e) Methyl-4-[(2-carbomethoxyethyl)thio]-5(Z)-octadecenoate 19(e)

A mixture of tridecyltriphenyl phosphonium bromide (1.27 g; 2.4 mmol) and THF (20 ml) was allowed to stir for 3 minutes at room temperature. The solution was then cooled to -68°C , at which time n-butyllithium (1.05 ml; 2.4 mmol) was added slowly while maintaining a reaction temperature less than -65°C . Following stirring at -68°C the reaction was permitted to warm to -10°C for approximately 10 minutes. Upon recooling to -68°C , (0.05 g; 2.0 mmol) of 19(d) was dissolved in THF (10 ml) and slowly added. The reaction was stirred for one hour at -68°C followed by removal of the bath. Product was then triturated into hexane and also into ether, hexane and ether fractions were combined, evaporated to dryness and the remaining residue was flash chromatographed affording the desired octadecenoate.

1 (f) 4-[(2-Carboxyethyl)thio]-5(Z)-octadecenoic acid
(319 mg; 0.826 mmol) of 19(e) was dissolved in
methanol (7.5 ml) and permitted to stir under argon at
0°C. A 1N solution of sodium hydroxide (3.1 ml; 3.08
5 mmol) was added dropwise. The ice bath was then removed
and the reaction allowed to warm to room temperature for
approximately three hours. After which it was placed in
the refrigerator and stored overnight. Most of the
methanol was then evaporated and the aqueous residue was
10 cooled in an ice bath followed by acidification with
dilute HCl. The aqueous phase was extracted twice with
diethyl ether. The ether extracts were then combined and
dried over magnesium sulfate, filtered and evaporated to
give crude product. This was then recrystallized from
15 diethyl ether-hexane to afford the final product, mp 81°C;
Anal. Calcd C: 65.24; H: 9.91; S: 8.29; Found C: 65.50;
H: 10.05; S: 8.61.

EXAMPLE 20

As a specific embodiment of a composition of this
20 invention, an active ingredient, such as the compound of
Example 4(i), is dissolved in sterile water at a
concentration of 0.5 percent and aerosolized from a
nebulizer operating at an air flow adjusted to deliver the
desired aerosolized weight of drug.

25 EXAMPLE 21

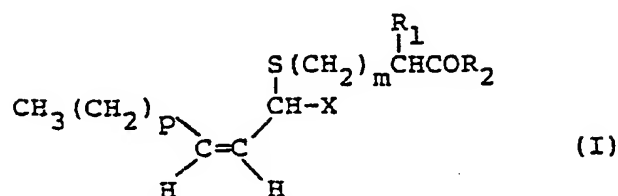
As an additional specific embodiment of a
composition of this invention, an active ingredient, such
as the compound of Example 5, is admixed with mannitol at
a concentration of 1.0 percent and administered from a
30 powder inhalation device adjusted to deliver the desired
weight of drug.

For: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

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What is claimed is:

1. A compound represented by the formula (I)



wherein m is 0, 1 or 2; p is 9, 10, 11, 12 or 13; R₁ is hydrogen, amino or ---NHCOCH_3 ; R₂ is hydroxyl, amino, $\text{---NHCH}_2\text{CO}_2\text{H}$, $\text{---NCH}_2\text{CO}_2\text{H}$, $\text{---NHCHCO}_2\text{H}$, $\text{---NHCHCO}_2\text{H}$ or $\text{---NHCH}_2\text{CONH}_2$; and X is $\text{---CO}_2\text{H}$, $\text{---CH}_2\text{OH}$, $\text{---CHCH}_2\text{OH}$ or $\text{---CH}(\text{CH}_2)_n\text{COR}$, wherein n is 1 or 2, Y is hydrogen or hydroxyl and R is hydroxyl or amino with the proviso that when m is 0, R₁ is hydrogen, or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein X is $\text{---CO}_2\text{H}$, $\text{---CH}_2\text{OH}$ or $\text{---CHCH}_2\text{OH}$.

3. A compound of Claim 2 which is
2-[(2-carboxyethyl)thio]-3(Z)-hexadecenoic acid,
2-[(2-carboxyethyl)thio]-3(Z)-hexadecen-1-ol
or
3-[(2-carboxyethyl)thio]-4(Z)-heptadecen-1,2-diol.

4. A compound of Claim 1 wherein X is $\text{---CH}(\text{CH}_2)_n\text{COR}$.

5. A compound of Claim 4 wherein R is hydroxyl and Y is hydroxyl.

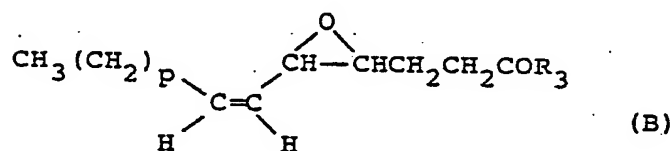
6. A compound of Claim 5 which is
4-hydroxy-5[(2-carboxyethyl)thio]-6(Z)-
nonadecenoic acid,
5[(3-carboxymethylamino-3-oxopropyl)-
thio]-4-hydroxy-6(Z)-nonadecenoic acid,
5[(3-carboxymethyl-N-methylamino-3-oxopropyl)-
thio]-4-hydroxy-6(Z)-nonadecenoic acid,
5[(2-amino-3-carboxamidomethylamino-3-oxo-
propyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid,
4-hydroxy-5-[(carboxymethyl)thio]-6(Z)-
nonadecenoic acid,
5-[[(2-aminocarbonyl)ethyl]thio]-4-hydroxy-6(Z)-
nonadecenoic acid,
4-hydroxy-5-[(2-amino-2-carboxyethyl)thio]-
6(Z)-nonadecenoic acid,
4(R)-hydroxy-5(S)-[(2-amino-2-carboxyethyl)-
thio]-6(Z)-nonadecenoic acid,
4(S)-hydroxy-5(R)-[(2-amino-2-carboxyethyl)-
thio]-6(Z)-nonadecenoic acid, or
4-hydroxy-5-[(3-carboxypropyl)thio]-6(Z)-
nonadecenoic acid.
7. A compound of Claim 5 which is
5[(2-amino-3-carboxymethylamino-3-oxopropyl)-
thio]-4-hydroxy-6(Z)-nonadecenoic acid,
5(S)-[(2-amino-3-carboxymethylamino-3-
oxopropyl)thio]-4(R)-hydroxy-6(Z)-nonadecenoic acid, or
5(R)-[(2-amino-3-carboxymethylamino-3-
oxopropyl)thio]-4(S)-hydroxy-6(Z)-nonadecenoic acid.
8. A compound of Claim 5 which is
3-hydroxy-4-[(2-carboxyethyl)thio]-5(Z)-
octadecenoic acid,
4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-
heptadecenoic acid, or
4-hydroxy-5[(2-carboxyethyl)thio]-6(Z)-
heneicosenoic acid.

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9. A compound of Claim 4 which is
 4[(2-carboxyethyl)thio]-5(Z)-octadecenoic acid,
 5[(2-carboxyethyl)thio]-6(Z)-nonadecenoic acid,
 5[(3-carboxymethylamino-3-oxopropyl)thio]-4-
 hydroxy-6(Z)-nonadecenamide, or
 4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-
 nonadecenamide.

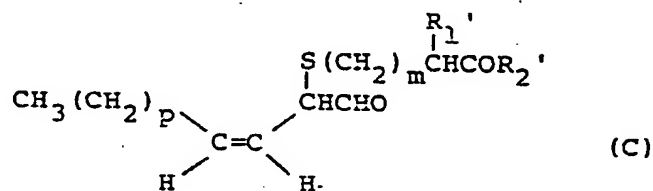
10. A pharmaceutical composition for inhibiting
 the effects of leukotriene in subjects in need of such
 inhibition comprising a pharmaceutical carrier or diluent
 and a nontoxic amount sufficient to produce said inhibition
 of a compound of Claim 1.

11. A compound of the formula (B)



wherein p is 9, 10, 11, 12 or 13 and R₃ is hydroxyl,
 amino or Oalk wherein alk is an alkyl radical containing
 one to six carbon atoms.

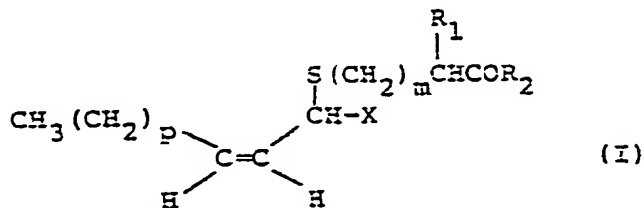
12. A compound of the formula (C)



wherein m is 0, 1 or 2; p is 9, 10, 11, 12 or 13; R₁' is
 hydrogen, --NHCCF_3 or --NHCCCH_3 and R₂' is amino,

$-\text{NHCH}_2\text{CO}_2\text{R}_3'$, $-\text{NCH}_2\text{CO}_2\text{R}_3'$, $-\text{NHCHCO}_2\text{R}_3'$, $-\text{NHCHCO}_2\text{R}_3'$,
 CH_3 CH_3 $\text{CH}(\text{CH}_2)_3$
 $-\text{NHCH}_2\text{CONH}_2$ or OR_3' wherein R_3' is an alkyl radical containing one to six carbon atoms with the proviso that when m is 0, R_1' is hydrogen.

13. A process for preparing the compounds represented by the formula (I)



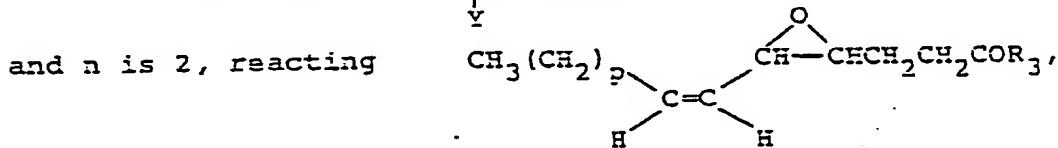
wherein m is 0, 1 or 2; p is 9, 10, 11, 12 or 13; R_1 is

hydrogen, amino or $-\text{NHCC}(=\text{O})\text{CH}_3$; R_2 is hydroxyl, amino, $-\text{NHCH}_2\text{CO}_2\text{H}$, $-\text{NCH}_2\text{CO}_2\text{H}$, $-\text{NHCHCO}_2\text{H}$, $-\text{NHCHCO}_2\text{H}$ or
 CH_3 CH_3 $\text{CH}(\text{CH}_3)_2$
 $-\text{NHCH}_2\text{CONH}_2$ and X is $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_2\text{OH})_2$ or
 OH

$-\text{CH}(\text{CH}_2)_n\text{COR}$, wherein n is 1 or 2, Y is hydrogen or

hydroxyl and R is hydroxyl or amino with the proviso that when m is 0, R_1 is hydrogen, or a pharmaceutically acceptable salt thereof which comprises:

(A) when X is $-\text{CH}(\text{CH}_2)_n\text{COR}$ wherein Y is hydroxyl

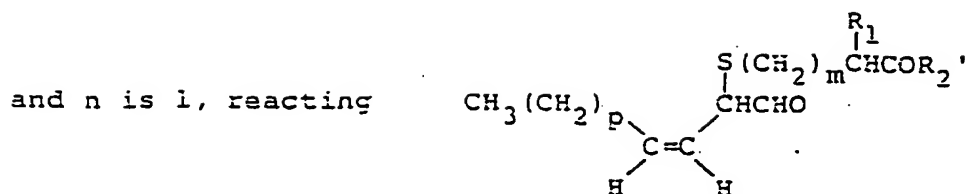


wherein R_3 is R or a radical easily convertible into R with

$\text{HS}(\text{CH}_2)_n\text{CHCOR}_2'$, wherein R_1' and R_2' are respectively R_1 and R_2 or a radical easily convertible into R_1 and R_2 ;

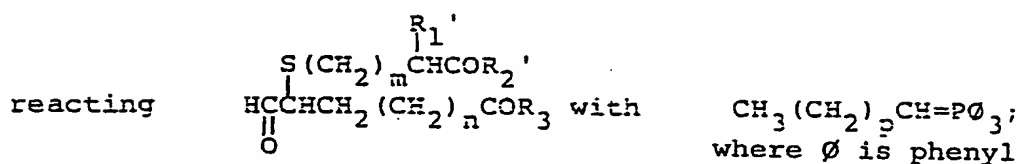
(B) when X is $-\text{CH}(\text{CH}_2)_n\text{COR}$ wherein Y is hydroxyl

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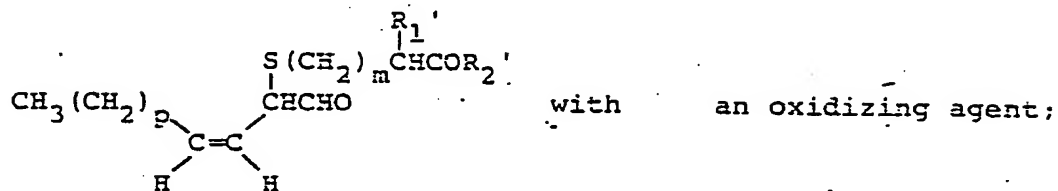


with CH_3COR_3 ;

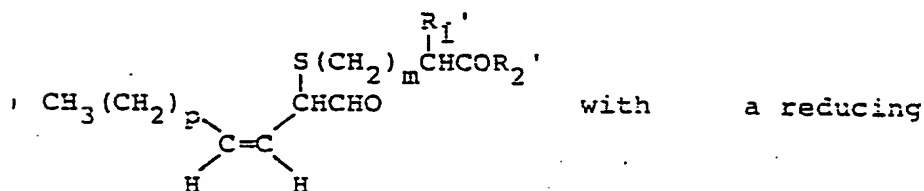
(C) when X is $\begin{array}{c} -\text{CH}(\text{CH}_2)_n\text{COR} \\ | \\ \text{Y} \end{array}$ wherein Y is hydrogen,



(D) when X is $-\text{CO}_2\text{H}$, reacting

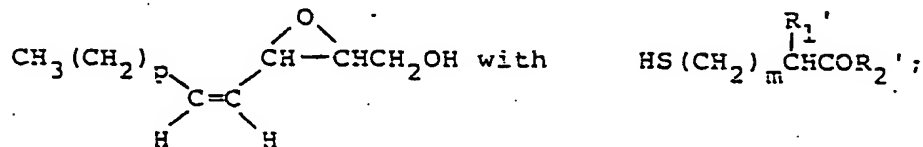


(E) when X is $-\text{CH}_2\text{OH}$, reacting



agent; or

(F) when X is $\begin{array}{c} -\text{CHCH}_2\text{OH} \\ | \\ \text{OH} \end{array}$, reacting



and then optionally converting R_1' , R_2' and R_3 into R_1 , R_2 and R and optionally forming the pharmaceutically acceptable salt of the compounds.

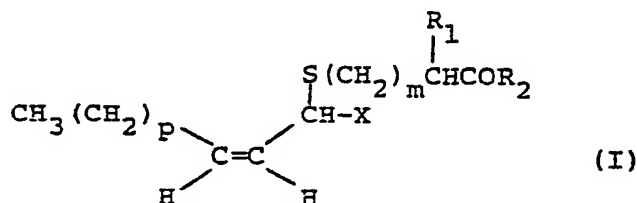
14. A compound of formula (I) as claimed in any of claims 1 to 9 for use as an active therapeutic substance.
15. A compound of formula (I) as claimed in any of claims 1 to 9 for use as an anti-asthmatic agent.

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For: AT

What is claimed is:

1. A process for preparing the compounds represented by the formula (I)



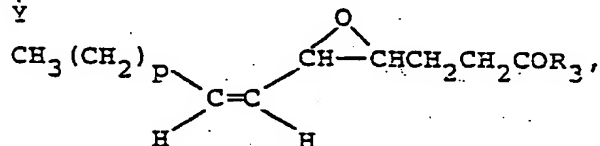
wherein m is 0, 1 or 2; p is 9, 10, 11, 12 or 13; R₁ is

hydrogen, amino or $\text{-NHCH}_2\text{CO}_2\text{H}$; R₂ is hydroxyl, amino, $\text{-NHCH}_2\text{CO}_2\text{H}$, $\text{-NCH}_2\text{CO}_2\text{H}$, $\text{-NHCHCO}_2\text{H}$, $\text{-NHCHCO}_2\text{H}$ or $\text{-NHCH}_2\text{CO}_2\text{H}$; and X is $\text{-CO}_2\text{H}$, $\text{-CH}_2\text{OH}$, $\text{-CHCH}_2\text{OH}$ or $\text{-CH(CH}_2)_n\text{COR}$, wherein n is 1 or 2, Y is hydrogen or

hydroxyl and R is hydroxyl or amino with the proviso that when m is 0, R₁ is hydrogen, or a pharmaceutically acceptable salt thereof which comprises:

(A) when X is $\text{-CH(CH}_2)_n\text{COR}$ wherein Y is hydroxyl

and n is 2, reacting

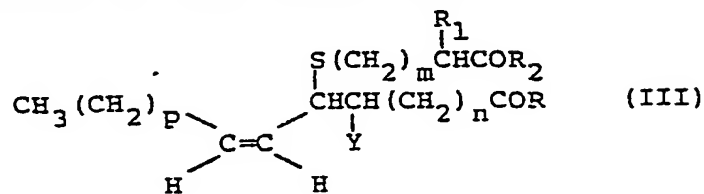


wherein R₃ is R' or a radical easily convertible into R with

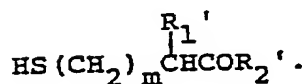
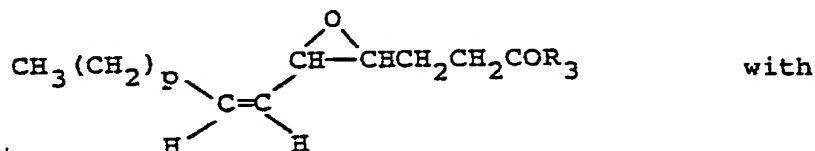
$\text{HS(CH}_2)_n\text{CHCOR}_2'$, wherein R₁' and R₂' are respectively R₁ and R₂ or a radical easily convertible into R₁ and R₂;

(B) when X is $\text{-CH(CH}_2)_n\text{COR}$ wherein Y is hydroxyl

2. A process according to Claim 1 for preparing the compounds of the formula (III)



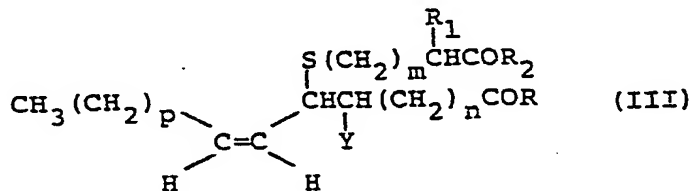
wherein n is 2 and Y is hydroxyl, which comprises reacting

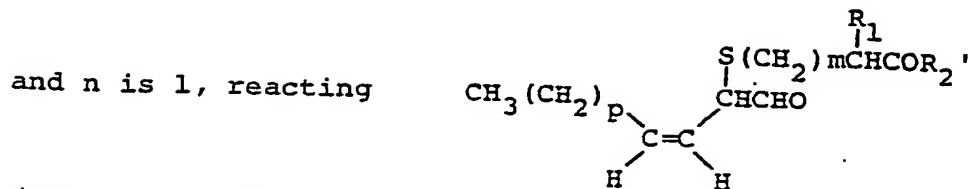


3. A process according to Claim 2 for preparing 5-[(2-amino-3-carboxymethylamino-3-oxopropyl)thio]-4-hydroxy-6(Z)-nonadecenoic acid which comprises reacting methyl 4,5-epoxy-6(Z)-nonadecenoate with 2-trifluoroacetamido-3-carbomethoxymethylamino-3-oxopropylmercaptan and converting the resultant compound with aqueous base to the desired product.

4. A process according to Claim 2 for preparing 4-hydroxy-5-[(2-carboxyethyl)thio]-6(Z)-nonadecenoic acid which comprises reacting methyl 4,5-epoxy-6(Z)-nonadecenoate with methyl-3-mercaptopropionate and converting the resultant compound with aqueous base to the desired product.

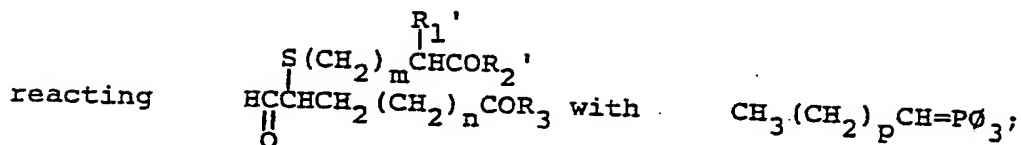
5. A process according to Claim 1 for preparing the compounds of the formula (III)



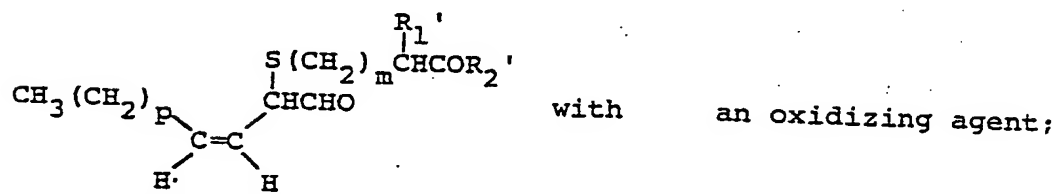


with CH_3COR_3 ;

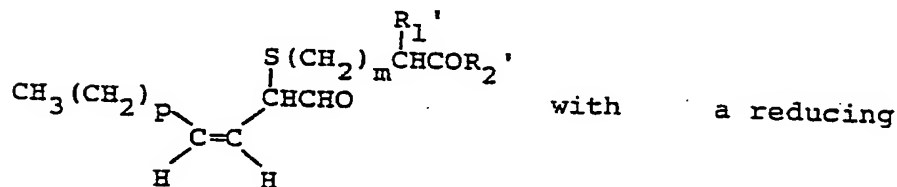
(C) when X is $\begin{array}{c} -\text{CH}(\text{CH}_2)_n\text{COR} \\ \text{Y} \end{array}$ wherein Y is hydrogen,



(D) when X is $-\text{CO}_2\text{H}$, reacting

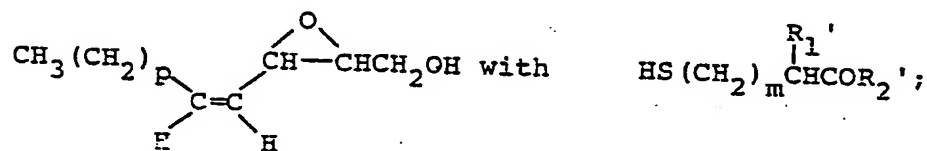


(E) when X is $-\text{CH}_2\text{OH}$, reacting



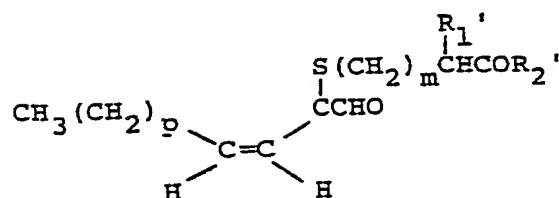
agent; or

(F) when X is $\begin{array}{c} -\text{CHCH}_2\text{OH} \\ \text{OH} \end{array}$, reacting



and then optionally converting R_1' , R_2' and R_3 into R_1 , R_2 and R and optionally forming the pharmaceutically acceptable salt of the compounds.

wherein n is 1 and Y is hydroxyl which comprises reacting

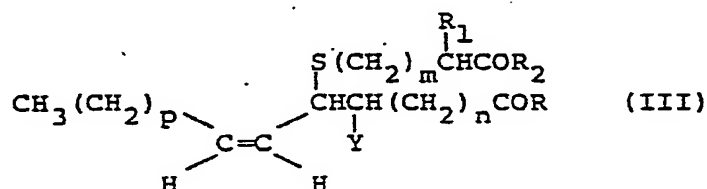


with

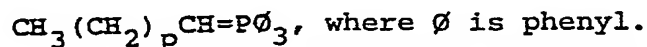
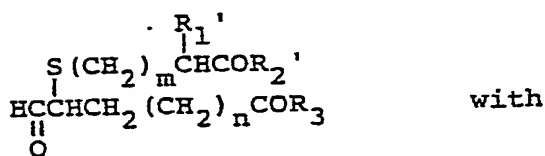


6. A process according to Claim 5 for preparing 3-hydroxy-4-[(2-carboxyethyl)thio]-5(Z)-octadecenoic acid which comprises reacting 2-[(2-carboxyethyl)thio]-hexadec-3(Z)-enal with methyl acetate and converting the resultant compound with aqueous base to the desired product.

7. A process according to Claim 1 for preparing the compounds of the formula (III)



wherein Y is hydrogen which comprises reacting



8. A process according to Claim 7 for preparing 4-[(2-carboxyethyl)thio]-5(Z)-octadecenoic acid which comprises reacting methyl-4-[(2-carbomethoxyethyl)thio]-4-formylbutanoate with tridecyltriphenylphosphonium ylid and converting the resulting compound in aqueous base to the desired product.

9. A process for the preparation of a pharmaceutical composition which comprises combining a compound of formula (I) as defined in any of claims 1 to 8 with a pharmaceutically acceptable carrier therefor.